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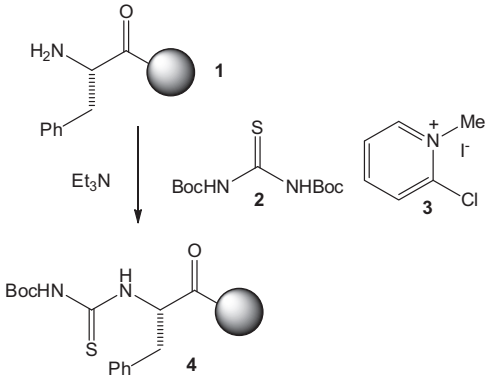
1. Current literature highlights

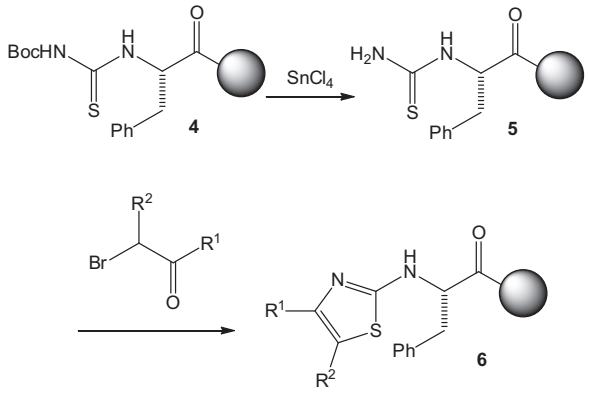
1.1. Solid-phase synthesis of peptide thioureas and thiazole-containing macrocycles

Thioureas occur in a number of biologically-active molecules, with a range of pharmacological properties including analgesic, anticancer, antifungal and antibacterial properties. In addition, thiourea derivatives are potent inhibitors of enzymatic targets for medical use. Thioureas can also be synthetically converted into thiazoles, a heterocycle that occurs both in nature and in many drug molecules. A recent paper has presented a novel method for the solid-phase synthesis of α-thiourea peptides, which were subsequently converted to thiazoles and incorporated into macrocyclic structures through ring-closing olefin metathesis [1].

The activation of *N,N'*-di-Boc-thiourea with $CuSO_4$, $HgCl_2$ or Mukaiyama's reagent is a well-known method for the generation of guanidines. However, it was found that conditions could be modified such that the major product of the reaction of the thiourea with a solid-supported amino acid was the thiourea peptide. For example, phenylalanine immobilised on 4-hydroxymethylbenzoic acid (HMBA) resin (**1**) was treated with a pre-mixed solution in dry DMF of *N,N'*-di-Boc-thiourea (**2**), Mukaiyama's reagent (**3**) and triethylamine to give predominantly the thiourea derivative (**4**) rather than a guanidine derivative.



With conditions having been optimised for formation of α-thiourea peptides, the approach was successfully tested on the range of 20 proteinogenic amino acids, generating products in good yield irrespective of the size and nature of the side-chains. Deprotection of the thiourea (removing the Boc group) proceeded cleanly by treating with dilute stannic chloride in dichloromethane to give **5**, and thiazole formation was achieved by the Hantzsch reaction with α-haloketones to give **6**.



The scene was now set to attempt the formation of macrocycles containing thiazoles. A small collection of thiazoles was prepared using the protocol outlined above. In particular, cyclisation to the thiazole using bromopyruvic acid generated carboxylated thiazoles (**7**) which could undergo amide-forming reactions with amines following on-resin activation. Having already incorporated an allylglycine residue on the carboxy-terminal side of the peptide, coupling with an alkene on the carboxylated thiazole to give **8**, permitted macrocyclisation to product **9** by ring closing metathesis (RCM). The RCM reaction was found to proceed most successfully with the Hoveyda Grubbs second generation catalyst, generating a range of macrocycles with from 15 to 17 atoms. It was found that the reaction was sufficiently flexible to prepare any of four possible diastereoisomers, in excellent product yields and purities.

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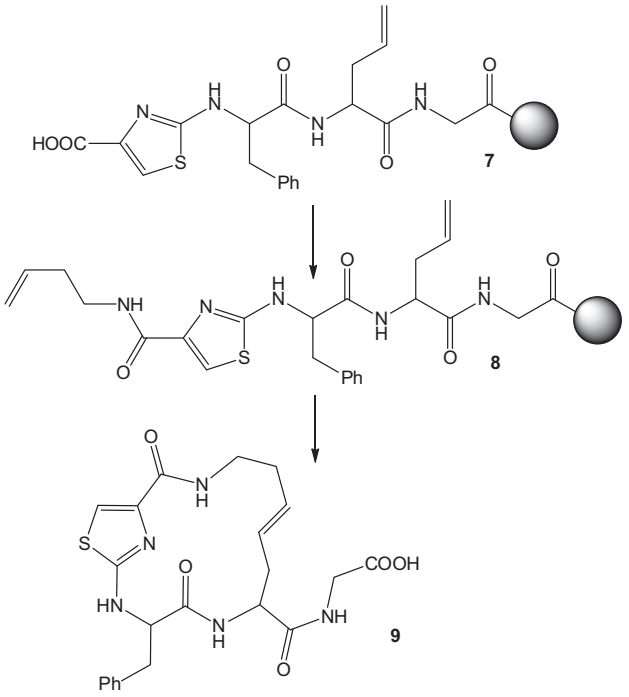

Overall, this new methodology provides a mild and selective approach to *N*-terminally modified α-thiourea peptides on solid support. The approach has further been used to prepare a number of thiazoles and thiazole-containing macrocycles by the RCM reaction.

2. A summary of the papers in this month's issue

2.1. Polymer supported synthesis

No papers this month.

2.2. Solution-phase synthesis

Multi-component reactions (MCRs) feature the potential for abundant reagent combinations, inputs, and post-MCR modifications, which result in exceptionally high diversification power. An expeditious cascade protocol for the synthesis of functionalised imidazo[1,2-*a*]pyridin-3-ols has been developed based on the Petasis reaction. With the availability of commercial reagents and high efficiency in expanding molecule diversity, this method offers advantages to the existing procedures for the synthesis of imidazo-pyridin-3-ol analogues [2].

A previously unknown class of highly substituted benzoquinoline–spirooxindoles has been easily prepared by a novel application of a mild and efficient catalyst, $SbCl_3$, for carbon–carbon and carbon–nitrogen bond formation reactions. The approach reacted isatins and alkynes (dialkyl but-2-ynedioate) with an aromatic amine (2-naphthylamine) in a one-pot three-component reaction to give a library of dialkyl 2′-oxo-4*H*-spiro[benzo[*f*]quinoline-3,3′-indoline]-1,2-dicarboxylate derivatives in very good to excellent yields [3].

An efficient synthesis of diverse 2-aryl/heteroaryl substituted pyrimidinyl ethanones has been developed using a palladium-catalyzed Suzuki–Miyaura coupling reaction strategy. Use of $Pd(OAc)_2$ in the presence of PPh_3 and Na_2CO_3 in 1,4-dioxane solvent was found to be the most effective reaction condition for this transformation [4].

The catalytic, highly regio-, diastereo-, and enantioselective synthesis of a small library of chiral spirooxindolopyrrolizidines has been described. This approach proceeds *via* a three-component 1,3-dipolar cycloaddition reaction of azomethine ylides, derived from isatin, with electron-deficient dipolarophiles, and 3-(2-alkenoyl)-1,3-oxazolidin-2-ones. A chiral copper(II) complex of cyclohexane-1,2-bis(arylmethyleneamine) catalysed this process at room temperature [5].

A domino reaction for the rapid and diverse synthesis of spiro[1*H*-pyrazolo[3,4-*b*]benzo[*h*]dihydroquinolin-4,3-indolin-2-ones] has been reported. The synthesis represents a thermodynamically-favoured four-component reaction between phenylhydrazine, isatins, naphthylamines, and 3-ketoesters giving novel products in excellent yields under solvent-free conditions [6].

2.3. Scaffolds and synthons for combinatorial libraries

The efficient synthesis of novel glycoconjugate amino acid building blocks wherein the amino acid and carbohydrate moieties are linked via a sulphonamide functional group has been reported. The general reaction sequence consists of coupling a glycosyl thioacetate to an amino acid methyl ester followed by oxidation and deprotection of the carbohydrate moiety. The synthesis of derivatives from a range of amino acids has been demonstrated, with reaction at either the α-amino group of amino acid precursors or the sidechain ε-amino group of lysine precursors [7].

2.4. Solid-phase supported reagents

In a recent paper, a variety of ketoximes, prepared from the corresponding ketones, undergo Beckmann rearrangement using $H_3PW_{12}O_{40}$ (DTPA) in acetonitrile under reflux to yield *N*-substituted amides and lactams in good to excellent yields (72–96%). The method provides an efficient, clean, eco-friendly, and simple synthesis, using a catalyst which is cheap, moisture tolerant, recoverable, and reusable without much loss of its activity [8].

An efficient one-pot synthesis of 2-substituted quinoxalines from 1,2-diamines and phenacyl bromides has been developed using K10-montmorillonite (K10 clay) as a catalyst at 50 °C in acetonitrile. The method offers an easy route for the synthesis of substituted quinoxalines in high yields, and a plausible mechanism has been proposed. Furthermore, the K10 clay catalyst can be recovered by simple filtration and reused six times without any loss in its catalytic activity [9].

The development of sustainable catalysts that can combine advantages from both homogeneous and heterogeneous catalysis has raised considerable promise over the last decade. To this end, using ligation chemistries that show high functional tolerance, that are highly efficient, specific, versatile, and that require mild conditions are particularly favoured. Following these guidelines, the copper-catalysed azide–alkyne cycloaddition reaction (CuAAC) has been employed for the heterogenisation of homogeneous catalysts [10].

2.5. Novel resins, linkers and techniques

No papers this month.

2.6. Library applications

A four-component Ugi reaction (Ugi-4CR) using formylphenyl boronic acids under mild conditions has been developed for the synthesis of arylboronic acid analogues. The reactions were performed in methanol and accelerated by microwave irradiation, which makes this strategy suitable for constructing

boronic-containing chemical libraries. Two of the synthesised analogues were found to have cytotoxic activity against HepG2, MDA-MB231, and A549 cancer cell lines, demonstrating the potential application of this approach in developing novel boron-containing pharmaceuticals [11].

With a broad spectrum of antiviral activity against clinically relevant mutant viruses, analogues from a new pyridone series met a mandatory criterion for next generation NNRTIs. Using a simple synthetic approach, a library of inhibitors was constructed, leading to the identification of a new pyridone. In cell cultures, this new NNRTI shows a superior potency profile against a range of wild type and clinically relevant, resistant mutant HIV viruses [12].

In an effort to improve a therapy for giardiasis and amoebic dysentery, the creation of chemical libraries is necessary to obtain novel drugs with high activity combined with low toxicity. The synthesis of novel 3-tetrazolylmethyl-4*H*-chromen-4-ones via an Ugi-azide multicomponent reaction and their biological evaluation against *Entamoeba histolytica*, *Giardia lamblia* and *Trichomona vaginalis* has been described. Biological results show that these compounds could be considered as candidates to anti-parasitic drugs, especially against *G. lamblia* [13].

Oroidin, (*E*)-*N*-(3-(2-amino-1*H*-imidazol-4-yl)allyl)-4,5-dibromo-1*H*-pyrrole-2-carboxamide, is a pyrrole alkaloid isolated from the marine sponge *Agelas oroides*. Routine screening in a panel of twelve cancer cell lines revealed the compound to be only poorly cytotoxic. The development of eight focused libraries comprising thirty compounds in total revealed two new compounds as potent inhibitors of cell growth in the panel of cell lines [14].

MurF ligase is a crucial enzyme that catalyses the ultimate intracellular step of bacterial peptidoglycan biosynthesis, and thus represents an attractive target for antibacterial drug discovery. The design, synthesis and evaluation of a new series of cyanothiophene-based inhibitors of MurF enzymes from *Streptococcus pneumoniae* and *Escherichia coli* have been described. Different structural modifications of the parent compounds resulted in a focused library of 37 new inhibitors, providing low micromolar inhibitors of MurF from *E. coli* and *S. pneumoniae* [15].

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